REMARKS

Claims 94-107 were pending in the application. Claims 95-98 have been canceled without prejudice. Claim 94 has been amended. Accordingly, claims 94 and 99-107 are pending in the application.

Claim 94 has been amended to incorporate the subject matter of claims 95-98, *i.e.*, to specify all six (6) heavy and light chain variable region CDR sequences.

No new matter has been added. The foregoing amendments should not be construed as an acquiescence to any of the Examiner's rejections, and are solely to expedite prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Rejection of Claims 94-107 Under 35 U.S.C. §112, First Paragraph- Written Description

Claims 94-107 are rejected as not meeting the written description requirement with regard to "conservative sequence modifications." Applicants respectfully traverse this rejection. In particular, Applicants disagree with the Examiner's statement that "[t]he claims encompass a potentially unlimited genus of antibodies . . ."

From the outset, the claimed CDR sequences are sequences of only 5-17 amino acid residues in length. Given that the claims are limited to "conservative amino acid modifications" of these sequences (*i.e.*, modifications that do not abrogate the binding of the antibody and include particular art-recognized amino acid substitutions having a similar side chain; see, *e.g.*, Stryer, *Biochemistry*, 2nd ed., Chapter 2, pages 13-15; enclosed as Appendix E), the modifications encompassed by the claims are clearly described, and are limited to a particular set of art-recognized amino acids. It is firmly established that it is not necessary to include information known in the art in a patent specification to meet the written description requirement. Specifically, in the recent decision of *Monsanto v. Mitchell*, 2006 U.S. App. LEXIS 20914 (Fed. Cir. August 16, 2006), the CAFC held that there is no need for known gene sequences to be disclosed in the specification to meet the written description requirement because the sequences were already known to those skilled in the art. The Court held, in particular, that "[g]iven the knowledge in the art, it was unnecessary for the '605 patent to include specific gene sequences when referring to the CaMV 35S promoter to meet the written description requirement." *Id.* at 17.

Similarly, in *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005), the claimed invention included claims to a chimeric gene comprising different gene segments which together encode a single-chain chimeric protein for expression on the surface of an immune cell. In *Capon*, the Federal Circuit determined that "the Board erred in ruling that §112 imposes a *per se* rule requiring recitation in the specification of the nucleotide sequence of the claimed DNA, when that sequence is already known in the field." *Id.* at 1360-1361. The Court explained that:

> [w]hen the prior art includes the nucleotide information, precedent does not set a *per se* rule that the information must be determined a fresh. Both parties state that a person experienced in the field of this invention would know that these known DNA segments would retain their DNA sequences when linked by known methods. Both parties explain that their invention is not in discovering which DNA segments are related to the immune response, for that is in the prior art, but in the novel combination of the DNA segments to achieve a novel result. *Id.* at 1358.

Like the claims at issue in *Monsanto* and *Capon*, the present claims are drawn to antibodies having conservative modifications of particular variable region amino acid sequences and, thus, encompass modifications that are already known in the art. Accordingly, it is not necessary that they be described in the present specification. Given that Applicants have described the parent CDR sequences and/or heavy and light chain variable regions sequences, one of ordinary skill could have readily determined which amino acid substitutions are being claimed based on what was well-known in the art. Indeed, at the time of filing, conservative sequence modifications were clearly known (see, *e.g.*, the Stryer reference cited above which describes and categorizes art-recognized amino acid substitutions having similar sidechains). This is further supported by the enclosed Declaration in which Dr. Tibor Keler testifies that the identification of conservative sequence modifications within the claimed variable region sequences that do not eliminate antigen binding was well-within the knowledge and skill of the art at the time the present application was filed.

Accordingly, based on the legal framework set forth in, *e.g.*, *Monsanto* and *Capon*, and the fact that the present claims are drawn to a limited set of art-recognized amino acid substitutions, the claims clearly meet the requirements for written description.

Rejection of Claims 94-107 Under 35 U.S.C. §112, First Paragraph

Claims 94-107 are rejected as not being enabled. Applicants respectfully traverse this rejection. First, Applicants note that the pending claims, as amended, are drawn to human

antibodies that bind human dendritic cells, and that are defined by at least all six (6) heavy and light chain variable region sequences. Therefore, the Examiner's rejection of antibodies containing less than the full complement of CDR sequences is now moot.

With regard to the "conservative sequence modifications" encompassed by the claimed antibodies, Applicants respectfully traverse the Examiner's position that "the claims recite no limitations on the number of amino acids that can be 'modified' . . ."

As discussed in detail above, the claimed antibodies, and portions thereof, are limited to particular sequences and conservative modifications thereof, which represent a limited, art-recognized group of amino acid modifications. The antibodies must also retain their antigen binding function. Accordingly, the claims do indeed recite a clear limitation on the number of amino acids that can be modified.

As further described in detail below, and in the enclosed Declaration by Dr. Keler, it was well within the ordinary skill in the art to identify and test amino acid residues within the CDR domains that are critical for antigen binding or are amenable to conservative modifications, *i.e.*, conservative modifications which do not abolish antigen binding. Moreover, the identification of such conservative modifications would not have required undue experimentation and, in fact, involve routine techniques such as those described in the present specification (see, *e.g.*, Example 2 (page 56, line 1 through page 63, line 2) regarding the binding characteristics of human antibodies which bind dendritic cells).

In particular, Brummell *et al.* ((1993) Biochem. 32:1180-1187; enclosed as Appendix B) used site-directed mutagenesis to examine the binding site of antibodies specific for *Salmonella*. Specifically, the CDR3 heavy chain domain was selected for study and a total of ninety (90) mutants were produced and screened by affinity electrophoresis / Western blots. Those of particular interest were further characterized by enzyme immunoassay and thermodynamic characterization by titration microcalorimetry. Brummell *et al.* found that antigen binding "was retained in a wide range of mutants with only one residue, Gly^{102H}, being irreplaceable."

Similarly, Kobayashi *et al.* ((1999) Protein Eng. 12(10):879-884), which was cited by the Examiner in the Office Action dated November 3, 2004 (and enclosed as Appendix C), describes further methods to determine binding abilities of various mutant antibodies and states that "conservative substitution of Trp H33 by Tyr or Phe resulted in [only] moderate losses of binding affinity; however, replacement by Ala [*i.e.*, a non-conservative modification] had a significantly larger impact." (Abstract, comments in square brackets added).

Burks *et al.* ((1997) PNAS USA 94:412-417; enclosed as Appendix D) used PCR mutagenesis with *in vitro* transcription/translation and ELISA for the rapid generation and characterization of antibody mutants. Specifically, the authors analyzed the role and plasticity of six key contact residues in the binding pocket of a single chain Fv antibody derived from the anti-digoxin 26-10 murine antibody. A total of 114 mutant antibodies were produced. Approximately 75% of the single amino acid mutants exhibited significant binding to one or more of the digoxin analogs, even though non-conservative sequence modifications were permitted.

Other methods known in the art at the time of filing for identifying residues critical for antibody binding included, for example, comparing the antibody heavy and light chain variable region sequences to their respective germline sequences to identify which residues were amenable to conservative modification and which were not, *i.e.*, which residues had been conserved and which had been somatically mutated to improve binding.

Accordingly, given the knowledge and high level of skill in the antibody art at the filing date of the present application, one of ordinary skill clearly could have predictably identified and made conservative sequence substitutions, without undue experimentation, within the claimed variable region and CDR sequences, which would not have removed binding of the antibody to dendritic cells.

Applicants respectfully remind the Examiner that the appropriate inquiry with respect to enablement in the present case is whether it would have required undue experimentation at the time of the invention to have identified residues critical for binding to human dendritic cells within the claims CDR and variable regions. As set forth above, it was well within the skill of the art to have identified such residues, particularly within relatively short variable and CDR regions.

Therefore, based at least on the foregoing, Applicants respectfully request reconsideration and withdrawal of this rejection.

Rejection of Claims 94-107 Under 35 U.S.C. §112, First Paragraph

Claims 94-107 are rejected as containing new matter. Applicants respectfully traverse this rejection. However, to expedite prosecution, claims 95-98 have been canceled without

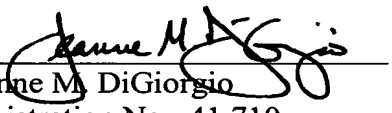
prejudice and independent claims 94 and 99 have been amended to specify the full complement (*i.e.*, all six (6)) of heavy and light chain variable region CDR sequences or by the full-length heavy and light chain variable region sequences. Therefore, this rejection is now moot.

CONCLUSION

In view of the above amendments and remarks set forth above, it is respectfully submitted that this application is in condition for allowance. If there are any remaining issues or the Examiner believes that a telephone conversation with Applicants' Attorney could be helpful in expediting prosecution of this application, the Examiner is invited to call the undersigned at (617) 227-7400.

Dated: September 29, 2006

Respectfully submitted,

By 

Jeanne M. DiGiorgio
Registration No.: 41,710
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, Massachusetts 02109
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant